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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

April 10, 2003

MEMORANDUM

SUBJECT: **MCPA**: Updating Executive Summary for Combined Chronic Toxicity/Carcinogenicity Study in Rat (MRID No. 40634101)

PC CODE: 030501 DP BARCODE: D289434
SUBMISSION NO.: S483005 TXR#: 0051487

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Special Review and Reregistration Division (7508C)

The study was previously reviewed by HED (TXR 0050852) and it was concluded that the NOAEL was 1.1 mg/lg/day and the LOAEL was 4.4 mg/kg/day based on increased SGPT levels, increased urea nitrogen levels and enlargement of the pituitary and adrenals. However, the HIARC evaluated the results of this study and determined that these changes were not supported by histopathology findings. Then, the HIARC raised NOAEL/LOAEL from 1.1/4.4 mg/kg/day to 4.4/17.6 mg/kg/day.

The new executive summary for the study is attached to this memorandum. The following is a citation of the study.

CITATION: Kirsch, P (1988) Study on the Chronic Toxicity and Oncogenic Potential of

MCPA in Rats. Department of Toxicology of BASF Aktiengesellshaft, Ludwigshafen/Rhein, FRG. Study No. 71S0045/8345. May 18, 1988. MRID No. 40634101. Unpublished.

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Supplement to Document Nos. 006793 and 0050852 - DER for MRID No. 40634101-40634105): MCPA Technical: Chronic Toxicity/Oncogenicity Feeding Study in Rats. This supplement provides a revised Executive Summary to upgrade the original DER.

EPA Reviewer: Paul Chin Signature: Paul Chin
Reregistration Action Branch 1, Health Effects Division (7509C) Date 4/10/03
EPA Secondary Reviewer: Whang Phang Signature: Whang Phang
Reregistration Action Branch 1, Health Effects Division (7509C) Date 4/10/03

TXR#: 0051487

DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/carcinogenicity [diet]-[rat]; OPPTS 870.4300 [§83-5]; OECD 453.

PC CODE: 030501 **DP BARCODE:** D289434
SUBMISSION NO.: S483005

TEST MATERIAL (PURITY): 4-chloro-2-methylphenoxyacetic acid (94.8% a.i.)

SYNONYMS: MCPA mix

CITATION: Kirsch, P (1988) Study on the Chronic Toxicity and Oncogenic Potential of MCPA in Rats. Department of Toxicology of BASF Aktiengesellshaft, Ludwigshafen/Rhein, FRG. Study No. 71S0045/8345. May 18, 1988. MRID No. 40634101. Unpublished.

EXECUTIVE SUMMARY:

In a combined chronic/carcinogenicity study (MRID No. 40634101), MPCA (Batch No: T. P. H. ; purity: 94.8% a.i.) was administered to Wistar rats (80/sex/dose) in the diet at levels of 0, 20, 80, or 320 ppm for 2 years (0, 1.1, 4.4, or 17.6 mg/kg/day in males and 1.4, 5.7, or 23 mg/kg/day in females). There were 50 rats/sex/dose in main study. There were 10 rats/sex/dose in a satellite I study of 52 weeks and 15 rats/sex/dose in a satellite II study of 2 years.

No treatment-related effects on survival and food consumption were seen either in the main study or in the satellite groups. Survival rate to 2 years was 60-67% in males and 67-87% in females.

No treatment-related effect was seen at 20 ppm.

At **80 ppm,** clinical signs of toxicity observed in both sexes of rats were swellings in

abdomen/increased abdominal circumference. **In males**, statistically significant decreases in triglycerides were observed at weeks 78 and 104. **In females**, there was a small, sporadic but statistically significant ($p<0.05$) elevation in body weights during the exposure period. In addition, decreases in triglycerides (at 52 and 78 weeks), elevation in SGPT values (at weeks 52 and 78; $p<0.05$), increases in urea nitrogen (at weeks 26, 52, and 78; $p<0.05$) and increase in incidence of enlargement of the pituitary and adrenals were observed (16/50 and 17/50 in mid dose tested vs 8/50 and 11/50 in controls). Although increased SGPT levels, increased urea nitrogen levels and increase in incidence of enlargement of the pituitary and adrenals were observed at 80 ppm, these effects are considered not to be treatment-related because these effects were not supported by histopathology findings.

At 320 ppm, clinical signs of toxicity included loss of hair (males only), conglutinations or colorations of the snout, eye or lower abdomen (males only), swellings in abdomen/increased abdominal circumference (both sexes), and general deteriorated state (both sexes). In males, minimal but statistically significant ($p<0.05$) depressions in body weights (3-9%) were observed early on (day 14) and throughout the study period up to terminal sacrifice. In contrast, in females, there was a small, sporadic but statistically significant ($p<0.05$) elevation in body weights during the exposure period.

In the 320 ppm **males**, statistically significant decreases in triglycerides were observed at weeks 78 and 104. Gross pathologic changes include increases in retraction and granular surface of the kidney. Microscopic pathologic changes include an increased incidence of more severe grades of chronic progressive nephropathy.

In the 320 ppm **females**, a minimal elevation ($p<0.05$) in clotting time was observed at both weeks 78 and 104. In addition, decreases in triglycerides (at 52 and 78 weeks) and elevation in SGPT values (at weeks 52, 78 and 104) were observed. In addition, increases in incidence of enlargement of the pituitary and adrenals were observed (20/50 and 23/50 in high dose tested vs 8/50 and 11/50 in controls).

The NOAEL for systemic toxicity was 80 ppm (4.4 in males and 5.7 mg/kg/day in females). The LOAEL for systemic toxicity was 320 ppm (17.6 in males and 23 mg/kg/day in females) based on increased SGPT levels in females and increased urea nitrogen levels in female. In addition, there was an increase in the retraction and granular surface of the kidney associated with an increase in the chronic progressive nephropathy in the males.

There was not a treatment-related increase in tumor incidence in any treated groups when compared to controls.

Dosing was considered adequate in this study based on nephrotoxicity observed in the 320 ppm males and females. There was an increase in the retraction and granular surface of the kidney associated with an increase in the chronic progressive nephropathy in the 320 ppm males. In

addition, treatment-related hepatotoxicity (increased SGPT levels and clotting time) was observed in this study.

This study is classified as Acceptable/Guideline and satisfies the Subdivision F guideline requirements for a combined chronic toxicity/carcinogenicity study (83-5) in rats.

It is noted that in the previous DER (TXR 0050852) the NOAEL was 1.1 mg/lg/day and the LOAEL was 4.4 mg/kg/day based on hepatotoxicity (increased SGPT levels), nephrotoxicity (increased urea nitrogen levels) and increase in enlargement of the pituitary and adrenals. However, these effects are considered not to be treatment-related because these observations were not supported by histopathology findings. Therefore, the HIARC raised NOAEL/LOAEL from 1.1/4.4 mg/kg/day to 4.4/17.6 mg/kg/day.

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Chemical: MCPA (and salts and esters)

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HED Records Reference Center
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